SEGMENT-SPECIFIC PULSE WAVE VELOCITY AND SUBCLINICAL CARDIAC OVERLOAD AND DAMAGE IN OLDER ADULTS: THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

by

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A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Health Science

Baltimore, Maryland

August, 2016

Abstract

Background: Arterial stiffness, often assessed as pulse wave velocity (PWV), independently predicts cardiovascular disease. However, few studies have explored the associations of segment-specific PWV measures with biomarkers of both cardiac overload (N-terminal pro-B-type natriuretic peptide, NT-proBNP) or damage (high sensitivity cardiac troponin T, hs-cTnT) among adults without clinical cardiovascular disease.

Methods: We examined PWV for six segments (cf [carotid-femoral], hc [heart-carotid], hf [heart-femoral], ha [heart-ankle], ba [brachial-ankle], and fa [femoral-ankle]) and their associations with NT-proBNP and hs-cTnT in 2,845 Caucasian and African American participants of the ARIC Study aged 67-90 years and without clinical history of cardiovascular disease. We conducted a cross-sectional analysis of data collected in 2011-13 using linear and logistic regression models with adjustment for demographic characteristics, traditional cardiovascular risk factors, and echo parameters of left ventricular (LV) remodeling and function.

Results: Most PWV measures demonstrated J- or U-shaped associations with NT-proBNP and hs-cTnT. Higher values of central PWV measures (cfPWV, hcPWV, and hfPWV) tended to be associated with higher levels of NT-proBNP, independently of demographic characteristics. The associations were attenuated after additional adjustment for clinical cardiovascular risk factors but remained borderline significant for hcPWV with NT-proBNP (but not with hs-cTnT). The other three PWV measures including peripheral elements (haPWV, baPWV, and faPWV) had overall less evident positive associations with cardiac biomarkers. faPWV, reflecting peripheral arterial stiffness, was inversely associated with both cardiac biomarkers. Inverse association that higher values of NT-proBNP in the lowest quartile than in the second quartile were

seen in six PWV measures and were most robust in PWV measures incorporating peripheral component.

Conclusion: Overall, the positive associations between PWV and cardiac biomarkers were more evident for central stiffness measures than for peripheral measures of PWV and were stronger for NT-proBNP than for hs-cTnT among this population of older adults without prevalent cardiovascular disease. Our findings suggest the importance of central arterial stiffness over peripheral arterial stiffness in the development of subclinical cardiac overload.

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Preface

I am interested in cardiac biomarkers and the association of arterial stiffness with cardiac biomarkers. It has been shown that the prevalence of arterial stiffness is high in older adults and arterial stiffness is involved at early stage of pathophysiological process to cardiac disease. Therefore, I was motivated to investigate the association of pulse wave velocity with cardiac overload (natriuretic peptide) and damage (cTnT). To our knowledge, this is the first study to comprehensively examine central and peripheral PWV measures with both NT-proBNP and hs-cTnT exclusively in older adults without prevalent cardiovascular disease. I hope our findings can contribute to future research in the relative field.

Acknowledgements

I would like to express my sincere gratitude to my advisor, Dr. Matsushita, for his excellent guidance and constant encouragement to my study and thesis project and for being caring about my well being all the time during my graduate program. He mentored and inspired me through his wisdom not only in academic research but also in life. I've learnt a lot from every meeting and discussion with Dr. Matsushita. I am also extremely grateful to my co-advisor, Dr. Selvin, for her tremendous support on my study and her insightful comments on my thesis. She gave me a great motivation towards the topic of cardiac biomarkers.

A special thank you to Aozhou Wu for his help and valuable suggestions on this project and to the ARIC writing group for their comments on the study proposal: Dr. Michelle Meyer, Dr. Susan Cheng, Dr. Ron C. Hoogeveen, Dr. Christie M. Ballantyne, Dr. Hirofumi Tanaka, and Dr. Gerardo Heiss.

I want to thank all the staff and participants of ARIC study for their important contributions. The Atherosclerosis Risk in Communities Study is carried out as a

collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

Most significantly, I would like to thank to my family for their unconditional love, constant support, and being the light of my life.

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Introduction

Arterial stiffness indicates increased rigidity and decreased elasticity of the arterial wall in response to blood pressure changes[1-3] and is considered as an important characteristic of aging process.[4] When arteries are stiff (less compliant), left ventricular (LV) end-systolic pressure increases and therefore the heart requires increased energy to ensure adequate blood output to the body.[4-5] Over time, this leads to LV hypertrophy, concentric remodeling,[6] and diastolic dysfunction.[5, 7] Indeed, parameters of arterial stiffness (particularly carotid-femoral pulse wave velocity [cfPWV] reflecting central arterial stiffness) are shown to independently predict cardiovascular disease (CVD).[8-11]

Indicating the involvement of arterial stiffness at early stage of pathophysiological process to cardiac disease, several studies have demonstrated the association between arterial stiffness and cardiac biomarkers including natriuretic peptides (BNP)[12-17] and cardiac troponin T (cTnT),[18-20] among those without clinical cardiac disease. However, only one of these studies analytically accounted for parameters of cardiac structure and function,[15] leaving uncertainty regarding whether arterial stiffness contributes to cardiac overload or damage before the manifestation of LV hypertrophy or remodeling. Also, most of these studies focused on either natriuretic peptides[12-17] or cTnT[18-20] (but not both) and were conducted in clinical populations[14-16, 19-20] (e.g., patients with hypertension[15-16, 19] or chronic kidney disease[14, 20]), and included a small number of participants (e.g., n< 1000).[13-16, 19-20] In addition, only a few prior studies have investigated arterial stiffness in multiple vascular beds.[12, 16]

Therefore, we undertook a cross-sectional study to examine the associations of segment-specific PWV measures, with biomarkers of both cardiac overload (natriuretic peptide) and damage (cTnT) in a large sample of community-dwelling older adults in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Study Population

The ARIC Study is a community-based cohort study originally designed to investigate risk factors for subclinical and clinical cardiovascular disease. The study recruited 15,792 participants aged 45-64 years at the baseline examination (visit 1) during 1987-1989 from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[21] The participants were invited for three short-term reexaminations, three years apart (visit 2 in 1990-1992, visit 3 in 1993-1995, and visit 4 in 1996-1998). Visit 5 took place from 2011-2013. A sixth visit is ongoing.

There were 6,538 participants who attended the fifth ARIC examination (visit 5) and were seen in the clinic between June 1, 2011 and August 30, 2013. At visit 5, the participants were aged 66-90 years and PWV was systematically assessed for the first time in the study. Of these 6,538 participants, we excluded 18 non-Caucasian/non-African American participants and 1,704 participants without any of six PWV measures. We also excluded 387 participants with clinical conditions questioning the validity of PWV measurement including BMI>40 or missing BMI (n=143), severe arrhythmias (n=133), self-reported aortic surgery (n=48), history of peripheral revascularization (n=24), aortic aneurysm (n=2), aortic stenosis and aortic regurgitation (n=34), and LV ejection fraction <30% (n=3). We additionally excluded 305 participants with any of cfPWV, hcPWV, hfPWV, or higher value of right and left of haPWV, baPWV and faPWV measures that were greater than 3 standard deviations from their respective means. Since we were interested in the association of arterial stiffness with cardiac biomarkers in the absence of clinical cardiovascular disease, we also excluded 611 participants with history of heart failure (prior hospitalization with heart failure or heart failure diagnosis confirmed with participants' physicians) or coronary heart disease (CHD) (self-reported

history at visit 1 or incident cases during follow-up prior to visit 5). We additionally excluded 95 participants missing NT-proBNP or hs-cTnT and 573 participants missing covariates of interest, leaving 2,845 participants for our analysis.

Pulse wave velocity

PWV is usually defined as the distance between two arterial sites divided by the time that it takes for the wave to travel that distance.[22] Using an oscillometry-based device, VP-1000plus (Omron Healthcare, Kyoto, Japan),[23-24] PWV was measured for the following segments: carotid-femoral (cf), heart-carotid (hc), heart-femoral (hf), heart-ankle (ha), brachial-ankle (ba), and femoral-ankle (fa). The measurement was repeated after 2-5 minutes and the mean PWV was recorded for each segment. Previous study stated acceptable repeatability for all PWV measures used in this study.[25] For haPWV, baPWV, and faPWV, we used the higher value of left and right PWV in our primary analyses. Given the measured segments, cfPWV, hfPWV, and hcPWV are considered to reflect central arterial stiffness, haPWV and baPWV reflect both central and peripheral arterial stiffness, and faPWV reflects peripheral arterial stiffness.[25-26]

Cardiac biomarkers

NT-proBNP, a biomarker of cardiac overload,[27] and high-sensitivity cTnT (hs-cTnT), a biomarker of subclinical cardiac damage,[28] were measured at visit 5 on the Roche Elecsys 2010 Analyzer (Roche Diagnostics, Indianapolis, IN 46250) using immunoassay method with sandwich principle.[23] The total duration of assay was 18 minutes.

Covariates of interest

All variables were collected at visit 5 except education level (high school or lower vs. college or above), which was recorded at visit 1. Age, gender, race, smoking status (current vs. former/never) and alcohol consumption (current vs. former/never) were self-reported. Body mass index was calculated by dividing weight (kg) by the square of

height (m). Total cholesterol was determined via an enzymatic determination method.[29] After a 5-minute rest, sitting blood pressure was measured three times using OMRON machine in the right arm (unless specific conditions prohibited using right arm), and the mean of the last two measurements was recorded. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or using medication for high blood pressure. Information on physical activity during leisure time was assessed as a composite score of frequency of TV viewing ("never" as score 5 and "very often" as 1), walking ("never" as score 1 and "very often" as 5), and bicycling ("never" as score 1 and "very often" as 5). Medication use in the past 4 weeks was based on 2004 med code including self-report or medication data files. Diabetes was defined as hemoglobin A1C ≥6.5%, fasting glucose ≥126 mg/dL, or using diabetic medication or self-report diagnosis of diabetes. Reduced kidney function was defined as creatinine-based estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2,[30] and urine albumin/creatinine ratio (ACR) ≥30 mg/g was considered as kidney damage.[31] LV hypertrophy was defined as LV mass index (LVMI) >115 g/m^2 for male and >95 g/m^2 for female.[32] Concentric remodeling was determined by relative wall thickness >0.42.[32] Diastolic dysfunction was measured as left atrial volume index (LAVI) ≥34 ml/m^2.[33] These three cardiac measures were based on echocardiogram during visit 5.

Statistical Analysis

Participants' median (interquartile interval) of NT-proBNP and hs-cTnT were calculated, respectively. Baseline characteristics of participants were compared across quartiles of each PWV measure, with a particularly focus on cfPWV since cfPWV has been regarded as a representative measure of arterial stiffness;[25, 34] differences were evaluated using ANOVA for continuous variables and the Pearson chi-squared test for categorical factors. Then, to evaluate the general pattern of the association of each PWV measure with NT-proBNP and hs-cTnT, we graphically displayed the mean levels of

each log-transformed cardiac biomarker adjusted to study averages of demographic variables (i.e., age, gender, race, education, and study center) using linear regression models. To allow for potential changes in slope, each PWV measure was modeled with linear spline terms with knots at the quartiles.

Since we observed non-linear relationships (often J- or U-shaped) in several combinations of PWV measures and cardiac biomarkers, subsequently every PWV measure was modeled with its quartiles to compare the strength of association across six PWV measures, with the second quartile as the reference. To assess the impact of potential confounders, we adjusted for three sets of covariates. Model 1 was adjusted for age, gender, race, education, and study center. Model 2 included all variables in Model 1 plus body mass index, systolic blood pressure, hypertension medication use, smoking status, alcohol consumption, physical activity, diabetes, total cholesterol, reduced kidney function, and kidney damage. Model 3 adjusted for all variables in Model 2 plus echo parameters of LV remodeling and function (LV hypertrophy, concentric remodeling, and diastolic dysfunction). We conducted analyses with NT-proBNP and hs-cTnT modeled as continuous independent variables with log-transformation (linear regression) and binary variables based on clinical cutpoints for elevations in each measure (i.e., NT-proBNP $\geq$300 vs <300 pg/ml [35-36] or hs-cTnT $\geq$14 vs <14 ng/L[37-39]) (logistic regression). All statistical analyses were performed using Stata version 13. P-values <0.05 were considered statistically significant. We also measured the correlation coefficients of six PWV measures.

Results

Among 2,845 participants, the mean age was 75.0 (SD 4.9) years, 62.3% (n=1,772) were female, and 23.2% (n=661) were African American. The median (interquartile interval) of NT-proBNP and hs-cTnT were 106.1 (57.6-200.9) pg/mL and 10.0 (7.0-14.0) ng/L, respectively. Baseline characteristics of our study population were summarized across the quartiles of cfPWV in Table 1. Compared to the participants in the lowest quartile (cfPWV $\leq$950.5 cm/s), those with higher cfPWV were more likely to be older, African American, and less educated and to have comorbidities such as hypertension, diabetes, reduced kidney function, and kidney damage. The prevalence of left ventricular hypertrophy and concentric remodeling were more common at higher values of cfPWV. Participants with higher values of other five PWV measures tended to be older and had higher systolic blood pressure compared to their counterparts with lower values but showed varying patterns for other factors (Supplementary Table 1-5). Specifically, the prevalence of diabetes, reduced kidney function, and kidney damage were positively correlated with hcPWV and hfPWV, but this pattern for haPWV and baPWV was evident only for the presence of kidney damage. In contrast, the prevalence of diabetes and reduced kidney function were inversely with faPWV (the prevalence of kidney damage was similar across the quartiles of faPWV). The prevalence of left ventricular hypertrophy and diastolic dysfunction were also inversely correlated with faPWV, whereas at least one of three cardiac echo parameters showed positive associations with the other four PWV measures.

Correlation coefficients of six PWV measures are summarized in Supplementary Table 6. The highest correlation was seen between two measures reflecting central stiffness, cfPWV and hfPWV (correlation coefficient of 0.853). Overall, hcPWV showed weak to modest correlations with all other five PWV measures, with the highest correlation of 0.427 with hfPWV. The three PWV measures that reflect peripheral

stiffness had moderate to strong correlations with each other (correlation coefficients ranging from 0.526 to 0.763). Of those peripheral measures, haPWV showed the strongest correlation with central measures, followed by baPWV. There was very weak correlation between faPWV and any of three central stiffness measures.

Figure 1 shows mean values of NT-proBNP and hs-cTnT according to six site-specific PWV measures after adjusting to average values of each demographic variable. For NT-proBNP, J- or U-shaped associations were observed for all the PWV measures except baPWV and faPWV, which overall demonstrated inverse associations. The slope for the association with NT-proBNP was steepest for hfPWV followed by cfPWV, hcPWV, and haPWV. The patterns in unadjusted models were generally consistent with that in the demographically adjusted models, although baPWV tended to show a U-shaped association in unadjusted model (Supplementary Figure 2). When we analyzed hs-cTnT, the associations were generally flatter (shallower slope) for every PWV compared to that for NT-proBNP.

Given the non-linear associations observed in Figure 1 (particularly for NT-proBNP), we subsequently modeled quartiles of each PWV measure with their second quartile as the reference and log-transformed NT-proBNP and hs-cTnT as continuous independent variables (Tables 2 and 3). When we adjusted for demographic variables (Model 1), the highest quartile (Q4) of PWV measures reflecting central arterial stiffness (cf, hc, and hf) as well as haPWV were significantly positively associated with higher values of NT-proBNP (Table 2). The third quartile (Q3) was significantly different only for hfPWV. Once we further adjusted for cardiovascular risk factors (Model 2 in Table 2), only the association for hcPWV remained borderline significant (p=0.094). However, this association was no longer borderline significant after additionally accounting for cardiac echo parameters (Model 3 in Table 2). faPWV, a measure of peripheral arterial stiffness, showed an inverse association with NT-proBNP. Significantly higher values of NT-

proBNP in the lowest quartile were seen not only in faPWV but also in haPWV and baPWV, two measures reflecting both central and peripheral arterial stiffness, as well as cfPWV (in Model 2) and hfPWV (in all Models).

Overall the associations of six PWV measures with hs-cTnT (Table 3) were less evident than those for NT-proBNP (Table 2). Specifically, the associations of the highest quartile (Q4) of cfPWV and hfPWV with higher levels of hs-cTnT were borderline significant (p value = 0.088 for cfPWV and p value =0.073 for hfPWV) in Model 1. Significantly higher value of hs-cTnT in the third quartile (Q3) but not in the highest quartile (Q4) was observed for baPWV in Model 1 and Model 3. faPWV was inversely correlated with hs-cTnT, with a significantly higher average value in the lowest quartile, in Model 1.

In analyses with NT-proBNP and hs-cTnT modeled as binary outcomes (NT-proBNP ≥300pg/ml (N=375) or hs-cTnT ≥14ng/L (N=768) (Tables 4 and 5), associations were less evident than in the continuous analyses (Tables 2 and 3). Nonetheless, the general patterns were similar, with positive associations between greater central stiffness measures and NT-proBNP (particularly hcPWV in Model 1) (Table 4). We also observed significantly higher odds of NT-proBNP elevation in the lowest vs. second quartile for some PWV measures, and more evident associations for NT-proBNP than for hs-cTnT overall.

Discussion

Among community-dwelling older adults without prevalent cardiovascular disease (heart failure or CHD), higher values of central PWV measures (cfPWV, hcPWV, and hfPWV) were associated with higher levels of NT-proBNP, independently of demographic characteristics. Although the associations were considerably attenuated after adjustment for traditional cardiovascular risk factors, the associations of hcPWV with higher levels of NT-proBNP (but not for hs-cTnT) remained borderline significant (but not after additionally accounting for LV remodeling). The positive associations of the other three PWV measures, including those that specifically reflect peripheral arterial stiffness (haPWV, baPWV, and faPWV), with cardiac biomarkers were overall less evident. FaPWV, which exclusively reflects peripheral stiffness, was overall inversely associated with both cardiac biomarkers. Of interest, higher values of NT-proBNP in the lowest quartile than in the second quartile were seen with most PWV measures, but this pattern was most consistent in PWV measures that incorporate a peripheral component.

To our knowledge, this is the first study to comprehensively examine central and peripheral PWV measures with both NT-proBNP and hs-cTnT exclusively in older adults without prevalent cardiovascular disease. Our main findings for the positive association between measures of central arterial stiffness and cardiac biomarkers are fundamentally consistent with previous studies.[14-18, 20] However, the associations in our study were overall weaker (i.e., borderline significant association seen only for hcPWV with NT-proBNP after adjusting for potential confounders) than some of the previous studies.[12, 16-18] PWV measurement issues are often important to consider when associations are weaker than expected. However it seems unlikely that it would be the case in the ARIC Study, since PWV was measured by trained and certified technicians using state-of-the art machines, with acceptable repeatability.[25] Our unique study population, exclusively

older Caucasian and African American (mean age of 75.0 years and age range 67-90 years), may play some role behind the weaker association. For example, arterial stiffness is very common at older ages, and thus, the variation of PWV measures may be reduced in older adults, potentially attenuating observed associations with risk factors in this specific population. Confirmatory investigations specifically in older adults are warranted, especially since a recent Chinese study with ~1,500 individuals reported opposite patterns: stronger associations of cfPWV with hs-cTnT levels in older adults (≥60 years) than in younger individuals (<60 years) with ours.[18]

We found the overall associations between central PWV measures (cfPWV, hcPWV, and hfPWV) with both NT-proBNP were more evident than that of PWV measures including peripheral element (haPWV, baPWV, and faPWV). This result was consistent with three previous studies[12, 16, 18] that investigated the association of both central and peripheral PWV measures with NT-proBNP or hs-cTnT. This observation may highlight the pathophysiological importance of central arterial stiffness over peripheral arterial stiffness. This finding is intuitive since central arteries are anatomically closest to the heart and their elasticity is key for effective cardiac function, i.e., ventricular-vascular coupling.[40] Thus, their abnormal changes may impact the heart more than that of more distal arteries such as the femoral and popliteal.[41-42]

The inverse associations we found between faPWV, the measure purely reflecting peripheral stiffness, with both cardiac biomarkers are consistent with previous studies. Although to our knowledge, our study is the first to show an inverse relationship for faPWV, two studies similarly reported such an inverse association for carotid-radial PWV (another measure of peripheral stiffness) among adults without cardiovascular disease.[12, 16] The pathophysiological meaning of this inverse correlation is not clear, but this finding may be related to the fact that the PWV value of the lower-limb arteries might be lower when significant stenosis exists in the leg arteries.[43] More specifically, some of

those in the lowest category of PWV may have peripheral artery disease, a condition prevalent in older adults[44] and known to be associated with high risk of heart failure.[45-46]

The associations with PWV measures were more evident for NT-proBNP than for hs-cTnT in our study. This observation is largely consistent with the only previous study simultaneously assessing both NT-proBNP and hs-cTnT for their associations with arterial stiffness.[47] This result is consistent with the concept of ventricular-vascular coupling as a key element behind the development of heart failure, as NT-proBNP is known to reflect volume overload and ventricular wall tension.[48] On the other hand, the actual mechanisms leading to the release of hs-cTnT to systemic circulation in persons without acute coronary syndrome are not well understood. Although future studies are needed for confirmation, our study suggests that neither of central nor peripheral arterial stiffness may play a pivotal role in the subclinical elevation of hs-cTnT, at least in older adults.

We found higher values of NT-proBNP in the lowest quartile compared to the second quartile for most central and peripheral PWV measures tested, resulting in overall J- or U-shaped associations between PWV and NT-proBNP. We did not find previous studies reporting a similar pattern for central PWV measures with NT-proBNP and the actual reasons of such an association are unclear. Nonetheless, there are a few plausible mechanisms. Such a J-shaped association between clinical characteristics and cardiovascular risk has been shown for various factors, like blood pressure,[49] glucose,[50] and adiposity.[51] Thus, there may be a group of individuals in the lowest quartile of PWV measures with latent high risk of cardiac conditions. Another possibility may be related to beneficial effects of natriuretic peptides, e.g., vasodilation and glucose utilization. So, it may be possible that in some individuals relatively high biological levels of natriuretic peptides lead to better artery function such as lower PWV values. Unfortunately, given

the cross-sectional design of the present study, we cannot elucidate the temporality of PWV and cardiac biomarkers.

Our findings may have several clinical and research implications. Although many parameters reflecting arterial stiffness have been proposed and are under investigation,[22] our results suggest the importance of focusing on those reflecting central arterial stiffness. Among parameters of central arterial stiffness, cfPWV has been considered as a gold standard.[52] However, our results of similar or sometimes stronger relationships of hcPWV and hfPWV over cfPWV suggest the potential usefulness of those alternative central measures for assessing cardiac health. Of note, hfPWV does not require carotid probe, which can sometimes be cumbersome to technicians and the subject, and thus may have technical advantage over cfPWV or hcPWV in some settings.

In addition to the inherent limitations of the cross-sectional design, there are a few other limitations of our study that should be considered in the interpretation of these data. As with any observational study, we cannot rule out the possibility of residual confounding. Also, generalization of our findings to younger population or ethnic groups other than Caucasian or African American may be problematic.

In conclusion, among older adults with high PWV values and without prevalent cardiovascular disease, central PWV measures (i.e., cfPWV, hcPWV and hfPWV) were associated with higher levels of NT-proBNP but not strongly associated with hs-cTnT. On the other hand, faPWV, which exclusively reflects peripheral arterial stiffness, was inversely associated with both cardiac biomarkers. Our study supports the pathophysiological importance of central arterial stiffness over peripheral arterial stiffness in the development of subclinical cardiac overload.

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Appendices

Main Tables and Figures

Table 1. Demographic and clinical characteristics of study participants overall and according to cfPWV quartile categories, ARIC visit 5 (2011-2013)

Variable	Overall (n=2845)	Q1: ≤950.5 cm/s (n=716)	Q2: 950.5-≤1122 cm/s (n=707)	Q3: 1122-≤1320.5 cm/s (n=711)	Q4:>1320.5 cm/s (n=711)	p-value
Age (years)	75.0 ± 4.9	73.4 ± 4.4	74.2 ± 4.6	75.5 ± 5.0	76.8 ± 5.1	**<0.001** *
Females, n (%)	1772 (62.3)	464 (64.8)	444 (62.8)	434 (61.0)	430 (60.5)	0.324
African American, n (%)	661 (23.2)	139 (19.4)	140 (19.8)	161 (22.6)	221 (31.1)	**<0.001** *
High school or lower education, n (%)	1524 (53.6)	335 (46.8)	370 (52.3)	388 (54.6)	431 (60.6)	**<0.001** *
Study center						**<0.001** *
Forsyth County, North Carolina	590 (20.7)	168 (23.5)	147 (20.8)	136 (19.1)	139 (19.6)	
Jackson, Mississippi	617 (21.7)	129 (18.0)	124 (17.5)	155 (21.8)	209 (29.4)	
Suburban Minneapolis, Minnesota	862 (27.3)	223 (31.2)	251 (35.5)	210 (29.5)	178 (25.0)	
Washington County, Maryland	776 (27.0)	196 (27.4)	185 (26.2)	210 (29.5)	185 (26.0)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	28.0 ± 4.3	28.4 ± 4.6	27.9 ± 4.4	27.6 ± 4.5	**0.020** *
Systolic blood pressure (mmHg)	130.4 ± 17.0	122.7 ± 15.2	128.4 ± 15.1	132.7 ± 16.2	137.8 ± 17.7	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	64.8 ± 9.5	66.9 ± 9.7	67.3 ± 10.1	67.6 ± 10.2	**<0.001** *
Antihypertensive medication, n (%)	1969 (69.2)	430 (60.1)	484 (68.5)	513 (72.2)	542 (76.2)	**<0.001** *
Diabetes, n (%)	956 (33.6)	178 (24.9)	227 (32.1)	242 (34.0)	309 (43.5)	**<0.001** *
Current smoker, n (%)	153 (5.4)	46 (6.4)	35 (5.0)	41 (5.8)	31 (4.4)	0.327
Current drinker, n (%)	1432 (50.3)	398 (55.6)	385 (54.5)	361 (50.8)	288 (40.5)	**<0.001** *
Physical activity score	2.3 ± 0.6	2.3 ± 0.6	2.4 ± 0.6	2.3 ± 0.6	2.2 ± 0.6	**<0.001** *
Total cholesterol (mmol/L)	4.8 ± 1.1	4.9 ± 1.0	4.9 ± 1.0	4.9 ± 1.1	4.8 ± 1.1	0.124
Reduced kidney function, n (%)	686 (24.1)	147 (20.5)	164 (23.2)	163 (22.9)	212 (29.8)	**<0.001** *
Kidney damage, n (%)	425 (14.9)	67 (9.4)	77 (10.9)	126 (17.7)	155 (21.8)	**<0.001** *
Left ventricular hypertrophy, n (%)	234 (8.2)	53 (7.4)	51 (7.2)	52 (7.3)	78 (11.0)	**0.024***
Concentric remodeling, n (%)	1274 (44.8)	277 (38.7)	319 (45.1)	312 (43.9)	366 (51.5)	**<0.001** *
Diastolic dysfunction, n (%)	288 (10.1)	78 (10.9)	65 (9.2)	74 (10.4)	71 (10.0)	0.749

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; cfPWV, carotid-femoral pulse wave velocity.

Table 2. Adjusted associations of measures of regional pulse wave velocity (in quartiles) with log NT-proBNP

	Regional PWV	PWV quartile categories [d]			
		Q1	Q2	Q3	Q4
		β[e](95%CI)	Ref	β(95%CI)	β(95%CI)
Model 1 [a]	cfPWV	0.074 (-0.018, 0.165)	0	-0.008 (-0.099, 0.084)	**0.131 (0.037, 0.225) ***
	hcPWV	0.039 (-0.053, 0.131)	0	0.053 (-0.039, 0.144)	**0.129 (0.036, 0.222) ***
	hfPWV	**0.151 (0.060, 0.243) ***	0	**0.106 (0.014, 0.197) ***	**0.209 (0.115, 0.303) ***
	haPWV	**0.104 (0.013, 0.196) ***	0	0.031 (-0.061, 0.123)	**0.098 (0.005, 0.191) ***
	baPWV	0.088 (-0.004, 0.179)	0	-0.003 (-0.094, 0.089)	0.044 (-0.050, 0.137)
	faPWV	0.079 (-0.012, 0.171)	0	0.008 (-0.084, 0.099)	-0.086 (-0.178, 0.006)
Model 2 [b]	cfPWV	**0.110 (0.021, 0.199) ***	0	-0.060 (-0.148, 0.029)	0.009 (-0.083, 0.102)
	hcPWV	0.050 (-0.039, 0.138)	0	0.020 (-0.069, 0.109)	0.077 (-0.013, 0.167)
	hfPWV	**0.199 (0.111, 0.288) ***	0	0.054 (-0.034, 0.143)	0.065 (-0.029, 0.158)
	haPWV	**0.150 (0.062, 0.239) ***	0	-0.035 (-0.124, 0.053)	-0.053 (-0.146, 0.040)
	baPWV	**0.139 (0.050, 0.228) ***	0	-0.064 (-0.152, 0.024)	-0.092 (-0.184, 0.001)
	faPWV	**0.115 (0.026, 0.203) ***	0	-0.021 (-0.108, 0.067)	**-0.138 (-0.228, -0.049) ***
Model 3 [c]	cfPWV	0.078 (-0.008, 0.164)	0	-0.057 (-0.143, 0.029)	0.024 (-0.066, 0.113)
	hcPWV	0.033 (-0.052, 0.119)	0	0.016 (-0.070, 0.101)	0.061 (-0.026, 0.148)
	hfPWV	**0.158 (0.072, 0.244) ***	0	0.037 (-0.049, 0.123)	0.075 (-0.016, 0.166)
	haPWV	**0.121 (0.036, 0.207) ***	0	-0.019 (-0.105, 0.066)	-0.032 (-0.122, 0.058)
	baPWV	**0.105 (0.018, 0.191) ***	0	-0.056 (-0.142, 0.029)	-0.063 (-0.152, 0.027)
	faPWV	**0.089 (0.003, 0.175) ***	0	-0.001 (-0.086, 0.084)	**-0.107 (-0.194, -0.021) ***

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; NT-pro BNP, N-terminal pro-B-type natriuretic peptide.

a. Model 1: Adjusted for demographic variables (age, race, gender, education level and center).

b. Model 2: Adjusted for covariates in Model 1 + other traditional cardiovascular risk factors (body mass index, systolic blood pressure, smoking status, alcohol habit, physical activity, diabetes, hypertensive medication, total cholesterol, kidney function, and kidney damage).

c. Model 3: Adjusted for covariates in Model 2 + cardiac echo parameters of left ventricular remodeling and function (left ventricular hypertrophy, concentric remodeling and diastolic dysfunction).

d. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)

hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)

hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)

baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

e. Linear regression coefficient indicates the difference in log NT-proBNP between each PWV quartile category and the reference category (Q2). Positive coefficient means higher log NT-proBNP level in the quartile category comparing to the reference group.

*P<0.05.

Table 3. Adjusted associations of measures of regional pulse wave velocity (in quartiles) with log hs-cTnT

	Regional PWV	PWV quartile categories [d]			
		Q1	Q2	Q3	Q4
		β[e](95%CI)	Ref	β(95%CI)	β(95%CI)
Model 1 [a]	cfPWV	-0.009 (-0.064, 0.047)	0	0.032 (-0.024, 0.087)	0.050 (-0.007, 0.106)
	hcPWV	-0.011 (-0.067, 0.044)	0	0.018 (-0.038, 0.074)	-0.002 (-0.058, 0.054)
	hfPWV	-0.005 (-0.061, 0.051)	0	0.008 (-0.048, 0.064)	0.052 (-0.005, 0.110)
	haPWV	0.041 (-0.014, 0.097)	0	0.014 (-0.042, 0.070)	-0.002 (-0.059, 0.054)
	baPWV	0.032 (-0.023, 0.088)	0	**0.058 (0.003, 0.114) ***	0.0001 (-0.056, 0.057)
	faPWV	**0.062 (0.007, 0.118) ***	0	-0.011 (-0.066, 0.045)	-0.039 (-0.095, 0.017)
Model 2 [b]	cfPWV	0.014 (-0.040, 0.068)	0	0.025 (-0.029, 0.079)	0.013 (-0.043, 0.069)
	hcPWV	-0.005 (-0.058, 0.049)	0	0.009 (-0.044, 0.063)	-0.016 (-0.070, 0.038)
	hfPWV	0.014 (-0.040, 0.067)	0	0.002 (-0.052, 0.056)	0.021 (-0.036, 0.077)
	haPWV	0.038 (-0.016, 0.091)	0	0.0001 (-0.053, 0.054)	-0.026 (-0.082, 0.030)
	baPWV	0.038 (-0.016, 0.092)	0	0.050 (-0.003, 0.104)	-0.010 (-0.066, 0.046)
	faPWV	0.049 (-0.005, 0.102)	0	-0.007 (-0.061, 0.046)	-0.021 (-0.075, 0.033)
Model 3 [c]	cfPWV	0.007 (-0.047, 0.060)	0	0.028 (-0.025, 0.082)	0.015 (-0.040, 0.071)
	hcPWV	-0.010 (-0.063, 0.043)	0	0.006 (-0.047, 0.059)	-0.019 (-0.073, 0.035)
	hfPWV	0.004 (-0.050, 0.057)	0	-0.003 (-0.056, 0.050)	0.023 (-0.033, 0.079)
	haPWV	0.028 (-0.025, 0.081)	0	0.004 (-0.050, 0.057)	-0.022 (-0.078, 0.034)
	baPWV	0.028 (-0.025, 0.081)	0	**0.053 (0.0001, 0.106) ***	-0.003 (-0.058, 0.053)
	faPWV	0.038 (-0.016, 0.091)	0	-0.004 (-0.057, 0.049)	-0.015 (-0.069, 0.038)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; hs-cTnT, high-sensitivity troponin T.

a. Model 1: Adjusted for demographic variables (age, race, gender, education level and center).

b. Model 2: Adjusted for covariates in Model 1 + other traditional cardiovascular risk factors (body mass index, systolic blood pressure, smoking status, alcohol habit, physical activity, diabetes, hypertensive medication, total cholesterol, kidney function, and kidney damage).

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hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)

baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

e. Linear regression coefficient: It indicates the difference in log hs-cTnT between each PWV quartile category and the reference category (Q2). Positive coefficient means higher log hs-cTnT level in the quartile category comparing to the reference group.

*P<0.05.

Table 4. Adjusted odds ratios (95% confidence intervals) of elevated NT-proBNP (≥300pg/ml) according to measures of regional pulse wave velocity (in quartiles)

	Regional PWV	PWV quartile categories [d]			
		Q1	Q2	Q3	Q4
		OR[e] (95%CI)	Ref	OR (95%CI)	OR (95%CI)
Model 1 [a]	cfPWV	1.185 (0.849, 1.654)	1	0.962 (0.690, 1.342)	1.344 (0.977, 1.848)
	hcPWV	**1.614 (1.166, 2.236) ***	1	1.251 (0.892, 1.754)	**1.472 (1.053, 2.059) ***
	hfPWV	1.153 (0.829, 1.604)	1	1.008 (0.725, 1.402)	1.327 (0.962, 1.831)
	haPWV	1.380 (0.995, 1.913)	1	1.024 (0.732, 1.434)	1.308 (0.948, 1.806)
	baPWV	1.322 (0.949, 1.841)	1	1.022 (0.734, 1.423)	1.180 (0.857, 1.626)
	faPWV	1.174 (0.855, 1.613)	1	1.083 (0.788, 1.488)	0.853 (0.853, 1.184)
Model 2 [b]	cfPWV	1.322 (0.934, 1.871)	1	0.858 (0.607, 1.211)	1.029 (0.734, 1.441)
	hcPWV	**1.700 (1.216, 2.377) ***	1	1.155 (0.814, 1.638)	1.302 (0.919, 1.845)
	hfPWV	1.298 (0.920, 1.830)	1	0.901 (0.640, 1.267)	0.949 (0.673, 1.339)
	haPWV	**1.546 (1.098, 2.178) ***	1	0.895 (0.632, 1.268)	0.964 (0.682, 1.362)
	baPWV	**1.486 (1.050, 2.102) ***	1	0.907 (0.644, 1.279)	0.899 (0.637, 1.267)
	faPWV	1.260 (0.902, 1.759)	1	1.046 (0.753, 1.454)	0.785 (0.557, 1.107)
Model 3 [c]	cfPWV	1.256 (0.876, 1.800)	1	0.890 (0.624, 1.270)	1.095 (0.773, 1.550)
	hcPWV	**1.643 (1.164, 2.319) ***	1	1.126 (0.785, 1.615)	1.255 (0.876, 1.796)
	hfPWV	1.180 (0.828, 1.681)	1	0.845 (0.594, 1.202)	0.984 (0.691, 1.401)
	haPWV	1.425 (0.999, 2.031)	1	0.933 (0.653, 1.333)	1.012 (0.710, 1.444)
	baPWV	1.357 (0.948, 1.943)	1	0.932 (0.655, 1.326)	0.983 (0.689, 1.401)
	faPWV	1.143 (0.808, 1.616)	1	1.116 (0.796, 1.565)	0.830 (0.584, 1.181)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; NT-pro BNP, N-terminal pro-B-type natriuretic peptide.

a. Model 1: Adjusted for demographic variables (age, race, gender, education level and center).

b. Model 2: Adjusted for covariates in Model 1 + other traditional cardiovascular risk factors (body mass index, systolic blood pressure, smoking status, alcohol habit, physical activity, diabetes, hypertensive medication, total cholesterol, kidney function, and kidney damage).

c. Model 3: Adjusted for covariates in Model 2 + cardiac echo parameters of left ventricular remodeling and function (left ventricular hypertrophy, concentric remodeling and diastolic dysfunction).

d. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)

hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)

hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)
baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

e. Odds ratio in logistic regression: It indicates the ratio of odds for elevated NT-proBNP level between each PWV quartile category and the reference category (Q2). Odds ratio > 1 means higher odds for elevated NT-proBNP level in the quartile category comparing to the reference group.

*P<0.05.

Table 5. Adjusted odds ratios (95% confidence intervals) of elevated hs-cTnT (≥14 ng/L) according to measures of regional pulse wave (in quartiles)

	Regional PWV	PWV quartile categories [d]			
		Q1	Q2	Q3	Q4
		OR[e] (95%CI)	Ref	OR (95%CI)	OR (95%CI)
Model 1 [a]	cfPWV	1.043 (0.797, 1.364)	1	1.135 (0.877, 1.469)	**1.307 (1.011, 1.690) ***
	hcPWV	0.947 (0.723, 1.241)	1	1.143 (0.887, 1.471)	0.989 (0.766, 1.277)
	hfPWV	1.067 (0.815, 1.399)	1	1.053 (0.812, 1.364)	1.241 (0.961, 1.603)
	haPWV	1.216 (0.934, 1.583)	1	1.060 (0.818, 1.374)	1.121 (0.867, 1.449)
	baPWV	1.058 (0.814, 1.377)	1	1.094 (0.849, 1.409)	1.011 (0.781, 1.308)
	faPWV	**1.344 (1.043, 1.732) ***	1	1.073 (0.829, 1.389)	0.996 (0.767, 1.294)
Model 2 [b]	cfPWV	1.125 (0.849, 1.491)	1	1.116 (0.853, 1.460)	1.168 (0.890, 1.532)
	hcPWV	0.986 (0.746, 1.304)	1	1.114 (0.857, 1.447)	0.923 (0.707, 1.205)
	hfPWV	1.130 (0.853, 1.498)	1	1.026 (0.784, 1.342)	1.089 (0.828, 1.431)
	haPWV	1.204 (0.913, 1.587)	1	1.038 (0.794, 1.358)	1.053 (0.799, 1.388)
	baPWV	1.063 (0.808, 1.399)	1	1.078 (0.828, 1.402)	0.972 (0.738, 1.280)
	faPWV	1.259 (0.966, 1.642)	1	1.110 (0.850, 1.450)	1.069 (0.813, 1.405)
Model 3 [c]	cfPWV	1.088 (0.819, 1.446)	1	1.123 (0.857, 1.472)	1.187 (0.903, 1.561)
	hcPWV	0.963 (0.727, 1.276)	1	1.103 (0.847, 1.437)	0.903 (0.691, 1.181)
	hfPWV	1.077 (0.811, 1.431)	1	1.001 (0.763, 1.312)	1.096 (0.833, 1.443)
	haPWV	1.170 (0.885, 1.546)	1	1.059 (0.809, 1.388)	1.079 (0.817, 1.424)
	baPWV	1.021 (0.774, 1.348)	1	1.087 (0.834, 1.417)	1.006 (0.763, 1.328)
	faPWV	1.210 (0.926, 1.581)	1	1.124 (0.859, 1.472)	1.106 (0.839, 1.457)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; hs-cTnT, high-sensitivity troponin T.

a. Model 1: Adjusted for demographic variables (age, race, gender, education level and center).

b. Model 2: Adjusted for covariates in Model 1 + other traditional cardiovascular risk factors (body mass index, systolic blood pressure, smoking status, alcohol habit, physical activity, diabetes, hypertensive medication, total cholesterol, kidney function, and kidney damage).

c. Model 3: Adjusted for covariates in Model 2 + cardiac echo parameters of left ventricular remodeling and function (left ventricular hypertrophy, concentric remodeling and diastolic dysfunction).

d. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)

hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)

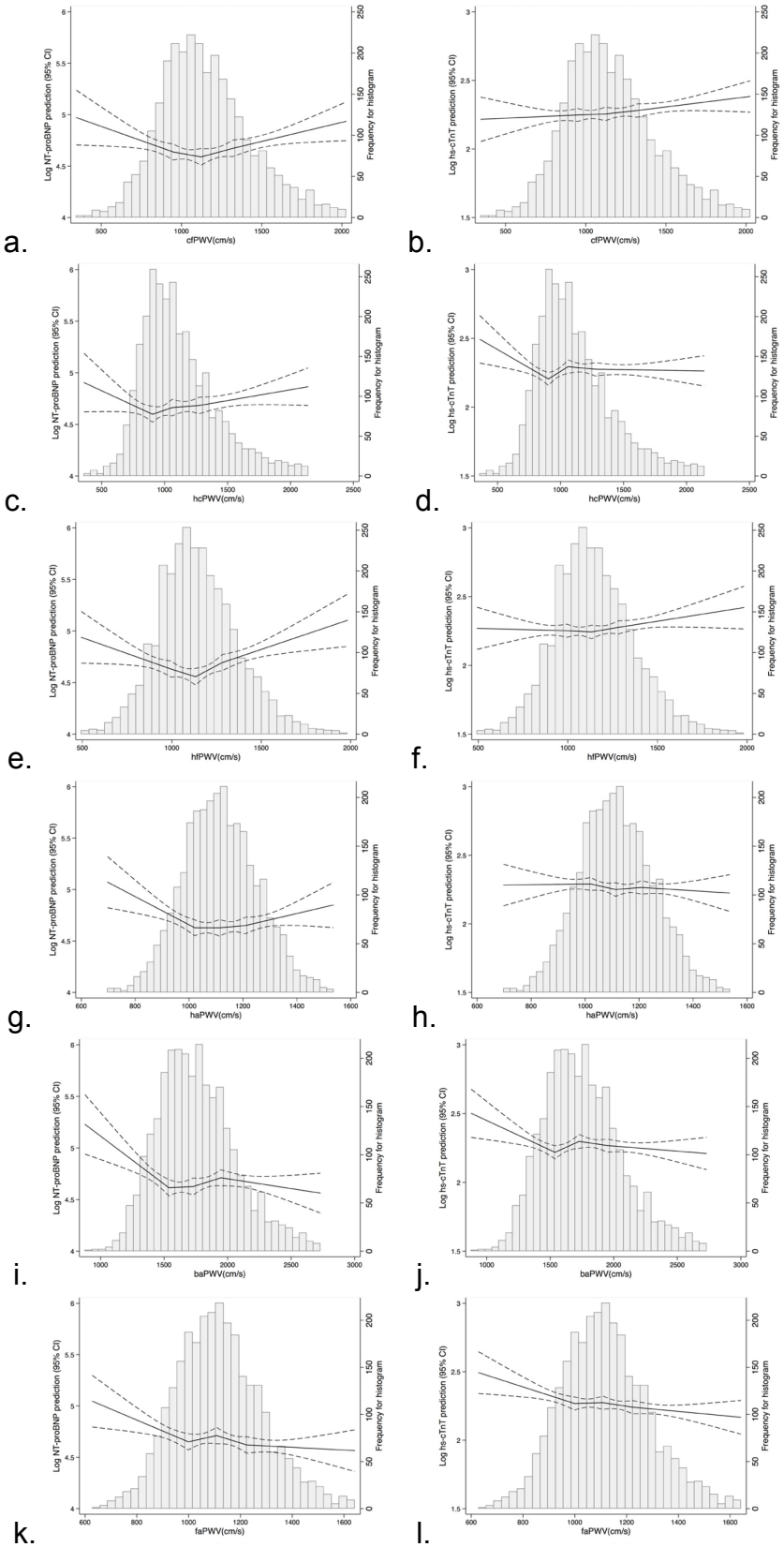
hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)
baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

e. Odds ratio in logistic regression: It indicates the ratio of odds for elevated hs-cTnT level between each PWV quartile category and the reference category (Q2). Odds ratio > 1 means higher odds for elevated hs-cTnT level in the quartile category comparing to the reference group.

*P<0.05.

Figure 1. Predicted log NT-proBNP and hs-cTnT with regional PWV with splines by quartiles adjusted for demographic characteristics (age, gender, race, education, center)



Supplement Tables and Figures

Supplementary Table 1. Demographic and clinical characteristics of study participants overall and according to hcPWV quartile categories, ARIC visit 5 (2011-2013)

Variable	Overall (n=2845)	Q1: ≤904 cm/s (n=712)	Q2: 904-≤1059.5 cm/s (n=712)	Q3: 1059.5 -≤1274.5 cm/s (n=710)	Q4: >1274.5 cm/s (n=711)	p-value
Age (years)	75.0 ± 4.9	74.5 ± 4.8	74.7 ± 5.1	75.2 ± 4.9	75.5 ± 4.9	**<0.001** *
Females, n (%)	1772 (62.3)	576 (80.9)	483 (67.8)	398 (56.1)	315 (44.3)	**<0.001** *
African American, n (%)	661 (23.2)	155 (21.8)	158 (22.2)	179 (25.2)	169 (23.8)	0.398
High school or lower education, n (%)	1524 (53.6)	409 (57.4)	374 (52.5)	387 (54.5)	354 (49.8)	**0.030** *
Study center						0.305
Forsyth County, North Carolina	590 (20.7)	136 (19.1)	170 (23.9)	149 (21.0)	135 (19.0)	
Jackson, Mississippi	617 (21.7)	151 (21.2)	148 (20.8)	163 (23.0)	155 (21.8)	
Suburban Minneapolis, Minnesota	862 (27.3)	227 (31.9)	217 (30.5)	197 (27.8)	221 (31.1)	
Washington County, Maryland	776 (27.0)	198 (27.8)	177 (24.9)	201 (28.3)	200 (28.1)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	27.9 ± 4.8	28.1 ± 4.6	27.9 ± 4.3	27.9 ± 4.2	0.875
Systolic blood pressure (mmHg)	130.4 ± 17.0	128.2 ± 17.0	129.0 ± 15.8	131.8 ± 17.3	132.6 ± 17.3	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	65.5 ± 9.7	66.7 ± 10.1	67.1 ± 9.6	67.4 ± 10.1	**0.002** *
Antihypertensive medication, n (%)	1969 (69.2)	490 (68.8)	496 (69.7)	496 (69.9)	487 (68.5)	0.934
Diabetes, n (%)	956 (33.6)	227 (31.9)	236 (33.1)	249 (35.1)	244 (34.3)	0.602
Current smoker, n (%)	153 (5.4)	42 (5.9)	44 (6.2)	32 (4.5)	35 (4.9)	0.453
Current drinker, n (%)	1432 (50.3)	346 (48.6)	350 (49.2)	361 (50.8)	375 (52.7)	0.395
Physical activity score	2.3 ± 0.6	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.6	0.669
Total cholesterol (mmol/L)	4.8 ± 1.1	5.0 ± 1.0	4.8 ± 1.0	4.8 ± 1.1	4.7 ± 1.1	**0.003** *
Reduced kidney function, n (%)	686 (24.1)	161 (22.6)	159 (22.3)	180 (25.4)	186 (26.2)	0.227
Kidney damage, n (%)	425 (14.9)	79 (11.1)	96 (13.5)	114 (16.1)	136 (19.1)	**<0.001** *
LV hypertrophy, n (%)	234 (8.2)	69 (9.7)	47 (6.6)	64 (9.0)	54 (7.6)	0.140
Concentric remodeling, n (%)	1274 (44.8)	319 (44.8)	324 (45.5)	331 (46.6)	300 (42.2)	0.385
Diastolic dysfunction, n (%)	288 (10.1)	69 (9.7)	66 (9.3)	68 (9.6)	85 (12.0)	0.312

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; hcPWV, heart-carotid pulse wave velocity.

Supplementary Table 2. Demographic and clinical characteristics of study participants overall and according to hfPWV quartile categories, ARIC visit 5 (2011-2013)

Variable	**Overall (n=2845)**	**Q1: ≤996 cm/s (n=712)**	**Q2: 996-≤1132.5 cm/s (n=711)**	**Q3: 1132.5-≤1282.5 cm/s (n=711)**	**Q4: >1282.5 cm/s (n=711)**	**p-value**
Age (years)	75.0 ± 4.9	73.4 ± 4.5	74.4 ± 4.6	75.3 ± 4.8	76.8 ± 5.2	**<0.001** *
Females, n (%)	1772 (62.3)	505 (70.9)	473 (66.5)	426 (59.9)	368 (51.8)	**<0.001** *
African American, n (%)	661 (23.2)	132 (18.5)	135 (19.0)	164 (23.1)	230 (32.3)	**<0.001** *
High school or lower education, n (%)	1524 (53.6)	378 (53.1)	359 (50.5)	390 (54.9)	397 (55.8)	0.194
Study center						**<0.001** *
Forsyth County, North Carolina	590 (20.7)	140 (19.7)	172 (24.2)	140 (19.7)	138 (19.4)	
Jackson, Mississippi	617 (21.7)	125 (17.6)	123 (17.3)	155 (21.8)	214 (30.1)	
Suburban Minneapolis, Minnesota	862 (27.3)	209 (29.4)	214 (30.1)	227 (31.9)	212 (29.8)	
Washington County, Maryland	776 (27.0)	238 (33.4)	202 (28.4)	189 (26.6)	147 (20.7)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	28.5 ± 4.4	28.1 ± 4.6	28.0 ± 4.5	27.2 ± 4.2	**<0.001** *
Systolic blood pressure (mmHg)	130.4 ± 17.0	123.0 ± 15.7	127.8 ± 14.5	132.5 ± 16.2	138.2 ± 17.6	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	64.6 ± 9.7	66.2 ± 9.6	67.6 ± 9.9	68.2 ± 10.1	**<0.001** *
Antihypertensive medication, n (%)	1969 (69.2)	453 (63.6)	486 (68.4)	501 (70.5)	529 (74.4)	**<0.001** *
Diabetes, n (%)	956 (33.6)	200 (28.1)	228 (32.1)	236 (33.2)	292 (41.1)	**<0.001** *
Current smoker, n (%)	153 (5.4)	49 (6.9)	31 (4.4)	36 (5.1)	37 (5.2)	0.188
Current drinker, n (%)	1432 (50.3)	387 (54.4)	367 (51.6)	364 (51.2)	314 (44.2)	**0.001** *
Physical activity score	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	2.3 ± 0.7	2.2 ± 0.6	**<0.001** *
Total cholesterol (mmol/L)	4.8 ± 1.1	4.9 ± 1.0	4.9 ± 1.0	4.8 ± 1.0	4.8 ± 1.1	0.259
Reduced kidney function, n (%)	686 (24.1)	143 (20.1)	163 (22.9)	169 (23.8)	211 (29.7)	**<0.001** *
Kidney damage, n (%)	425 (14.9)	65 (9.1)	83 (11.7)	112 (15.8)	165 (23.2)	**<0.001** *
LV hypertrophy, n (%)	234 (8.2)	57 (8.0)	54 (7.6)	58 (8.2)	65 (9.1)	0.749
Concentric remodeling, n (%)	1274 (44.8)	276 (38.8)	319 (44.9)	326 (45.9)	353 (49.6)	**0.001** *
Diastolic dysfunction, n (%)	288 (10.1)	81 (11.4)	50 (7.0)	87 (12.2)	70 (9.8)	**0.007** *

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; hfPWV, heart-femoral pulse wave velocity.

Supplementary Table 3. Demographic and clinical characteristics of study participants overall and according to haPWV quartile categories, ARIC visit 5 (2011-2013)

Variable	**Overall (n=2845)**	**Q1: ≤1021 cm/s (n=712)**	**Q2: 1021-≤1113 cm/s (n=713)**	**Q3: 1113-≤1208.5 cm/s (n=709)**	**Q4: >1208.5 cm/s (n=711)**	**p-value**
Age (years)	75.0 ± 4.9	73.7 ± 4.6	74.4 ± 4.7	75.1 ± 4.7	76.7 ± 5.2	**<0.001** *
Females, n (%)	1772 (62.3)	493 (69.2)	470 (65.9)	423 (59.7)	386 (54.3)	**<0.001** *
African American, n (%)	661 (23.2)	168 (23.6)	168 (23.6)	162 (22.8)	163 (22.9)	0.979
High school or lower education, n (%)	1524 (53.6)	377 (52.9)	388 (54.4)	370 (52.2)	389 (54.7)	0.745
Study center						**0.002** *
Forsyth County, North Carolina	590 (20.7)	136 (19.1)	120 (16.8)	165 (23.3)	169 (23.8)	
Jackson, Mississippi	617 (21.7)	155 (21.8)	161 (22.6)	150 (21.2)	151 (21.2)	
Suburban Minneapolis, Minnesota	862 (27.3)	195 (27.4)	232 (32.5)	208 (29.3)	227 (31.9)	
Washington County, Maryland	776 (27.0)	226 (31.7)	200 (28.1)	186 (26.2)	164 (23.1)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	29.0 ± 4.6	28.3 ± 4.5	27.7 ± 4.4	26.8 ± 4.1	**<0.001** *
Systolic blood pressure (mmHg)	130.4 ± 17.0	122.6 ± 15.3	128.1 ± 15.3	131.8 ± 15.4	139.1 ± 17.5	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	63.3 ± 9.4	66.0 ± 9.3	67.2 ± 9.5	70.2 ± 10.3	**<0.001** *
Antihypertensive medication, n (%)	1969 (69.2)	490 (68.8)	496 (69.6)	500 (70.5)	483 (67.9)	0.751
Diabetes, n (%)	956 (33.6)	228 (32.0)	244 (34.2)	231 (32.6)	253 (35.6)	0.475
Current smoker, n (%)	153 (5.4)	51 (7.2)	36 (5.0)	45 (6.3)	21 (3.0)	**0.003***
Current drinker, n (%)	1432 (50.3)	361 (50.7)	361 (50.6)	353 (49.8)	357 (50.2)	0.985
Physical activity score	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	0.367
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.0	4.9 ± 1.0	4.8 ± 1.1	4.8 ± 1.1	0.914
Reduced kidney function, n (%)	686 (24.1)	177 (24.9)	150 (21.0)	172 (24.3)	187 (26.3)	0.123
Kidney damage, n (%)	425 (14.9)	74 (10.4)	88 (12.3)	115 (16.2)	148 (20.8)	**<0.001** *
LV hypertrophy, n (%)	234 (8.2)	68 (9.6)	58 (8.1)	46 (6.5)	62 (8.7)	0.193
Concentric remodeling, n (%)	1274 (44.8)	300 (42.1)	306 (42.9)	330 (46.5)	338 (47.5)	0.107
Diastolic dysfunction, n (%)	288 (10.1)	82 (11.5)	65 (9.1)	68 (9.6)	73 (10.3)	0.466

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; haPWV, heart-ankle pulse wave velocity.

Supplementary Table 4. Demographic and clinical characteristics of study participants overall and according to baPWV quartile categories, ARIC visit 5 (2011-2013)

Characteristics	**Overall (n=2845)**	**Q1: ≤1538 cm/s (n=712)**	**Q2: 1538-≤1728 cm/s (n=711)**	**Q3: 1728-≤1948 cm/s (n=713)**	**Q4: >1948 cm/s (n=709)**	**p-value**
Age (years)	75.0 ± 4.9	73.3 ± 4.3	74.5 ± 4.8	75.4 ± 4.7	76.8 ± 5.2	**<0.001** *
Females, n (%)	1772 (62.3)	444 (62.4)	442 (62.2)	434 (60.9)	452 (63.8)	0.738
African American, n (%)	661 (23.2)	164 (23.0)	177 (24.9)	183 (25.7)	137 (19.3)	**0.023** *
High school or lower education, n (%)	1524 (53.6)	347 (48.7)	370 (52.0)	389 (54.6)	418 (59.0)	**0.001** *
Study center						**<0.001** *
Forsyth County, North Carolina	590 (20.7)	115 (16.2)	131 (18.4)	146 (20.5)	198 (27.9)	
Jackson, Mississippi	617 (21.7)	154 (21.6)	168 (23.6)	171 (24.0)	124 (17.5)	
Suburban Minneapolis, Minnesota	862 (27.3)	219 (30.8)	216 (30.4)	205 (28.8)	222 (31.3)	
Washington County, Maryland	776 (27.0)	224 (31.5)	196 (27.6)	191 (26.8)	165 (23.3)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	28.7 ± 4.8	28.3 ± 4.4	27.9 ± 4.4	26.9 ± 4.1	**<0.001** *
Systolic blood pressure (mmHg)	130.4 ± 17.0	121.8 ± 14.9	127.9 ± 14.7	133.0 ± 16.1	138.9 ± 17.3	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	64.2 ± 9.2	65.7 ± 9.5	67.6 ± 10.1	69.2 ± 10.2	**<0.001** *
Antihypertensive medication, n (%)	1969 (69.2)	475 (66.7)	493 (69.3)	512 (71.8)	489 (69.0)	0.224
Diabetes, n (%)	956 (33.6)	223 (31.3)	248 (34.9)	246 (34.5)	239 (33.7)	0.485
Current smoker, n (%)	153 (5.4)	58 (8.1)	30 (4.2)	38 (5.3)	27 (3.8)	**0.001** *
Current drinker, n (%)	1432 (50.3)	374 (52.5)	360 (50.6)	357 (50.1)	341 (48.1)	0.417
Physical activity score	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.6	2.2 ± 0.6	0.121
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.0	4.8 ± 1.0	4.8 ± 1.0	4.9 ± 1.1	0.403
Reduced kidney function, n (%)	686 (24.1)	172 (24.2)	163 (22.9)	172 (24.1)	179 (25.2)	0.790
Kidney damage, n (%)	425 (14.9)	70 (9.8)	95 (13.4)	122 (17.1)	138 (19.5)	**<0.001** *
LV hypertrophy, n (%)	234 (8.2)	62 (8.7)	52 (7.3)	57 (8.0)	63 (8.9)	0.691
Concentric remodeling, n (%)	1274 (44.8)	289 (40.6)	318 (44.7)	323 (45.3)	344 (48.5)	**0.027** *
Diastolic dysfunction, n (%)	288 (10.1)	83 (11.7)	69 (9.7)	73 (10.2)	63 (8.9)	0.364

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; baPWV, brachial-ankle pulse wave velocity.

Supplementary Table 5. Demographic and clinical characteristics of study participants overall and according to faPWV quartile categories, ARIC visit 5 (2011-2013)

Variable	**Overall (n=2845)**	**Q1: ≤999 cm/s (n=713)**	**Q2: 999-≤1108 cm/s (n=711)**	**Q3: 1108-≤1224 cm/s (n=713)**	**Q4: >1224 cm/s (n=708)**	**p-value**
Age (years)	75.0 ± 4.9	74.9 ± 4.9	74.5 ± 4.7	75.0 ± 5.0	75.6 ± 5.1	**0.001** *
Females, n (%)	1772 (62.3)	447 (62.7)	439 (61.7)	439 (61.6)	447 (63.1)	0.916
African American, n (%)	661 (23.2)	233 (32.7)	172 (24.2)	145 (20.3)	111 (15.7)	**<0.001** *
High school or lower education, n (%)	1524 (53.6)	394 (55.3)	362 (50.9)	364 (51.1)	404 (57.1)	**0.044***
Study center						**<0.001** *
Forsyth County, North Carolina	590 (20.7)	103 (14.5)	123 (17.3)	155 (21.7)	209 (29.5)	
Jackson, Mississippi	617 (21.7)	220 (30.9)	161 (22.6)	136 (19.1)	100 (14.1)	
Suburban Minneapolis, Minnesota	862 (27.3)	191 (26.8)	239 (33.6)	234 (32.8)	198 (28.0)	
Washington County, Maryland	776 (27.0)	199 (27.9)	188 (26.4)	188 (26.4)	201 (28.4)	
Body Mass Index (kg/m^2)	28.0 ± 4.5	29.3 ± 4.7	28.1 ± 4.5	27.5 ± 4.2	27.0 ± 4.1	**<0.001** *
Systolic blood pressure (mmHg)	130.4 ± 17.0	126.5 ± 16.5	128.9 ± 16.4	131.4 ± 16.3	134.8 ± 17.6	**<0.001** *
Diastolic blood pressure (mmHg)	66.7 ± 9.9	63.3 ± 9.3	65.4 ± 9.3	67.8 ± 9.6	70.1 ± 10.2	**<0.001** *
Antihypertensive medication, n (%)	1969 (69.2)	547 (76.7)	486 (68.4)	483 (67.7)	453 (64.0)	**<0.001** *
Diabetes, n (%)	956 (33.6)	271 (38.0)	247 (34.7)	229 (32.1)	209 (29.5)	**0.006***
Current smoker, n (%)	153 (5.4)	57 (8.0)	36 (5.1)	29 (4.1)	31 (4.4)	**0.004***
Current drinker, n (%)	1432 (50.3)	309 (43.3)	369 (51.9)	382 (53.6)	372 (52.5)	**<0.001** *
Physical activity score	2.3 ± 0.6	2.2 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	2.3 ± 0.6	**<0.001**
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.0	4.8 ± 1.0	4.8 ± 1.1	4.9 ± 1.1	**0.025** *
Reduced kidney function, n (%)	686 (24.1)	206 (28.9)	174 (24.5)	161 (22.6)	145 (20.5)	**0.002***
Kidney damage, n (%)	425 (14.9)	106 (14.9)	102 (14.3)	113 (15.8)	104 (14.7)	0.874
LV hypertrophy, n (%)	234 (8.2)	79 (11.1)	58 (8.2)	46 (6.5)	51 (7.2)	**0.009***
Concentric remodeling, n (%)	1274 (44.8)	327 (45.9)	291 (40.9)	325 (45.6)	331 (46.8)	0.116
Diastolic dysfunction, n (%)	288 (10.1)	96 (13.5)	69 (9.7)	67 (9.4)	56 (7.9)	**0.004***

Values are expressed as mean ± SD/median (IQR) for continuous variables, n (%) for categorical variables. * P <0.05 (two sided)
Abbreviations: SD, standard deviation; IQR, interquartile range; faPWV, femoral-ankle pulse wave velocity.

Supplementary Table 6. Correlation coefficients between PWV measures

	cfPWV	hcPWV	hfPWV	haPWV	baPWV	faPWV
cfPWV	1.000	0.016	0.853	0.655	0.506	-0.008
hcPWV	0.016	1.000	0.427	0.339	0.088	0.041
hfPWV	0.853	0.427	1.000	0.766	0.487	-0.001
haPWV	0.655	0.339	0.766	1.000	0.763	0.526
baPWV	0.506	0.088	0.487	0.763	1.000	0.610
faPWV	-0.008	0.041	-0.001	0.526	0.610	1.000

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV.

Supplementary Table 7. Unadjusted associations of measures of regional pulse wave velocity (in quartiles) with log NT-proBNP

	Regional PWV	PWV quartile categories [b]			
		Q1	Q2	Q3	Q4
		β[c] (95%CI)	Ref	β(95%CI)	β(95%CI)
Unadjusted model [a]	cfPWV	0.031 (-0.069, 0.130)	0	0.047 (-0.053, 0.146)	**0.222 (0.123, 0.322) ***
	hcPWV	0.086 (-0.013, 0.186)	0	0.032 (-0.068, 0.132)	0.085 (-0.015, 0.185)
	hfPWV	**0.121 (0.022, 0.220) ***	0	**0.117 (0.017, 0.216) ***	**0.234 (0.134, 0.333) ***
	haPWV	0.072 (-0.028, 0.171)	0	0.046 (-0.053, 0.146)	**0.185 (0.086, 0.285) ***
	baPWV	0.027 (-0.073, 0.126)	0	0.044 (-0.056, 0.143)	**0.200 (0.100, 0.299) ***
	faPWV	0.070 (-0.030, 0.169)	0	0.045 (-0.055, 0.145)	0.011 (-0.089, 0.111)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; NT-pro BNP, N-terminal pro-B-type natriuretic peptide.

a. Univariate linear regression with no adjustment.

b. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)
hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)
hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)
haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)
baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

c. Linear regression coefficient: It indicates the difference in log NT-proBNP between each PWV quartile category and the reference category (Q2). Positive coefficient means higher log NT-proBNP level in the quartile category comparing to the reference group.

*P<0.05.

Supplementary Table 8. Unadjusted associations of measures of regional pulse wave velocity (in quartiles) with log hs-cTnT

	Regional PWV	PWV quartile categories [b]			
		Q1	Q2	Q3	Q4
		β[c] (95%CI)	Ref	β(95%CI)	β(95%CI)
Unadjusted model [a]	cfPWV	-0.053 (-0.115, 0.009)	0	**0.095 (0.033, 0.157) ***	**0.183 (0.121, 0.246) ***
	hcPWV	**-0.064 (-0.126, -0.001) ***	0	**0.095 (0.033, 0.158) ***	**0.128 (0.066, 0.190) ***
	hfPWV	-0.055 (-0.117, 0.007)	0	**0.079 (0.017, 0.141) ***	**0.231 (0.169, 0.293) ***
	haPWV	-0.003 (-0.065, 0.060)	0	0.061 (-0.002, 0.123)	**0.130 (0.068, 0.193) ***
	baPWV	-0.020 (-0.082, 0.043)	0	**0.102 (0.039, 0.165) ***	**0.069 (0.006, 0.131) ***
	faPWV	**0.093 (0.030, 0.155) ***	0	-0.004 (-0.066, 0.059)	-0.025 (-0.088, 0.038)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; hs-cTnT, high-sensitivity troponin T.

Red & bold indicates statistically significant results.

a. Univariate linear regression with no adjustment.

b. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)

hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)

hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)

baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)

faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

c. Linear regression coefficient: It indicates the difference in log hs-cTnT between each PWV quartile category and the reference category (Q2). Positive coefficient means higher log hs-cTnT level in the quartile category comparing to the reference group.

*P<0.05.

Supplementary Table 9. Unadjusted odds ratios (95% confidence intervals) of elevated NT-proBNP (≥300pg/ml) according to measures of regional pulse wave velocity (in quartiles)

	Regional PWV	PWV quartile categories [b]			
		Q1	Q2	Q3	Q4
		OR[c] (95%CI)	Ref	OR (95%CI)	OR (95%CI)
Unadjusted model [a]	cfPWV	1.056 (0.763, 1.461)	1	1.093 (0.791, 1.510)	**1.639 (1.211, 2.220) ***
	hcPWV	**1.634 (1.192, 2.239) ***	1	1.255 (0.903, 1.743)	**1.449 (1.052, 1.998) ***
	hfPWV	1.053 (0.764, 1.451)	1	1.069 (0.776, 1.471)	**1.490 (1.101, 2.017) ***
	haPWV	1.251 (0.910, 1.718)	1	1.064 (0.767, 1.476)	**1.581 (1.163, 2.148) ***
	baPWV	1.141 (0.828, 1.573)	1	1.125 (0.816, 1.552)	**1.543 (1.136, 2.095) ***
	faPWV	1.155 (0.849, 1.571)	1	1.141 (0.839, 1.553)	1.005 (0.733, 1.378)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; NT-pro BNP, N-terminal pro-B-type natriuretic peptide.
Red & bold indicates statistically significant results.

a. Univariate logistic regression with no adjustment.

b. Quartiles for PWV measures:
cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)
hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)
hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)
haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)
baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)
faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

c. Odds ratio in logistic regression: It indicates the ratio of odds for elevated NT-proBNP level between each PWV quartile category and the reference category (Q2). Odds ratio > 1 means higher odds for elevated NT-proBNP level in the quartile category comparing to the reference group.

*P<0.05.

Supplementary Table 10. Unadjusted odds ratios (95% confidence intervals) of elevated hs-cTnT (≥14 ng/L) according to measures of regional pulse wave (in quartiles)

	Regional PWV	PWV quartile categories [b]			
		Q1	Q2	Q3	Q4
		OR[c] (95%CI)	Ref	OR (95%CI)	OR (95%CI)
Unadjusted model [a]	cfPWV	0.922 (0.718, 1.184)	1	**1.335 (1.051, 1.696) ***	**1.824 (1.445, 2.304) ***
	hcPWV	0.791 (0.616, 1.015)	1	**1.397 (1.107, 1.765) ***	**1.460 (1.157, 1.841) ***
	hfPWV	0.934 (0.726, 1.202)	1	**1.312 (1.031, 1.670) ***	**2.038 (1.614, 2.573) ***
	haPWV	1.058 (0.829, 1.350)	1	1.224 (0.963, 1.556)	**1.648 (1.305, 2.081) ***
	baPWV	0.897 (0.704, 1.142)	1	1.214 (0.962, 1.533)	1.241 (0.983, 1.567)
	faPWV	**1.385 (1.097, 1.748) ***	1	1.105 (0.871, 1.402)	1.060 (0.834, 1.347)

Abbreviations: PWV, pulse wave velocity; cfPWV, carotid-femoral PWV; hcPWV, heart-carotid PWV; hfPWV, heart-femoral PWV; haPWV, heart-ankle PWV; baPWV, brachial-ankle PWV; faPWV, femoral-ankle PWV; hs-cTnT, high-sensitivity troponin T.

Red & bold indicates statistically significant results.

a. Univariate logistic regression with no adjustment.

b. Quartiles for PWV measures:

cfPWV: Q1, ≤950.5 (n=716); Q2, 950.5-≤1122 (n=707); Q3, 1122-≤1320.5 (n=711); Q4, >1320.5 (n=711)

hcPWV: Q1, ≤904 (n=712); Q2, 904-≤1059.5 (n=712); Q3, 1059.5-≤1274.5 (n=710); Q4, >1274.5 (n=711)

hfPWV: Q1, ≤996 (n=712); Q2, 996-≤1132.5 (n=711); Q3, 1132.5-≤1282.5 (n=711); Q4, >1282.5 (n=711)

haPWV: Q1, ≤1021 (n=712); Q2, 1021-≤1113 (n=713); Q3, 1113-≤1208.5 (n=709); Q4, >1208.5 (n=711)

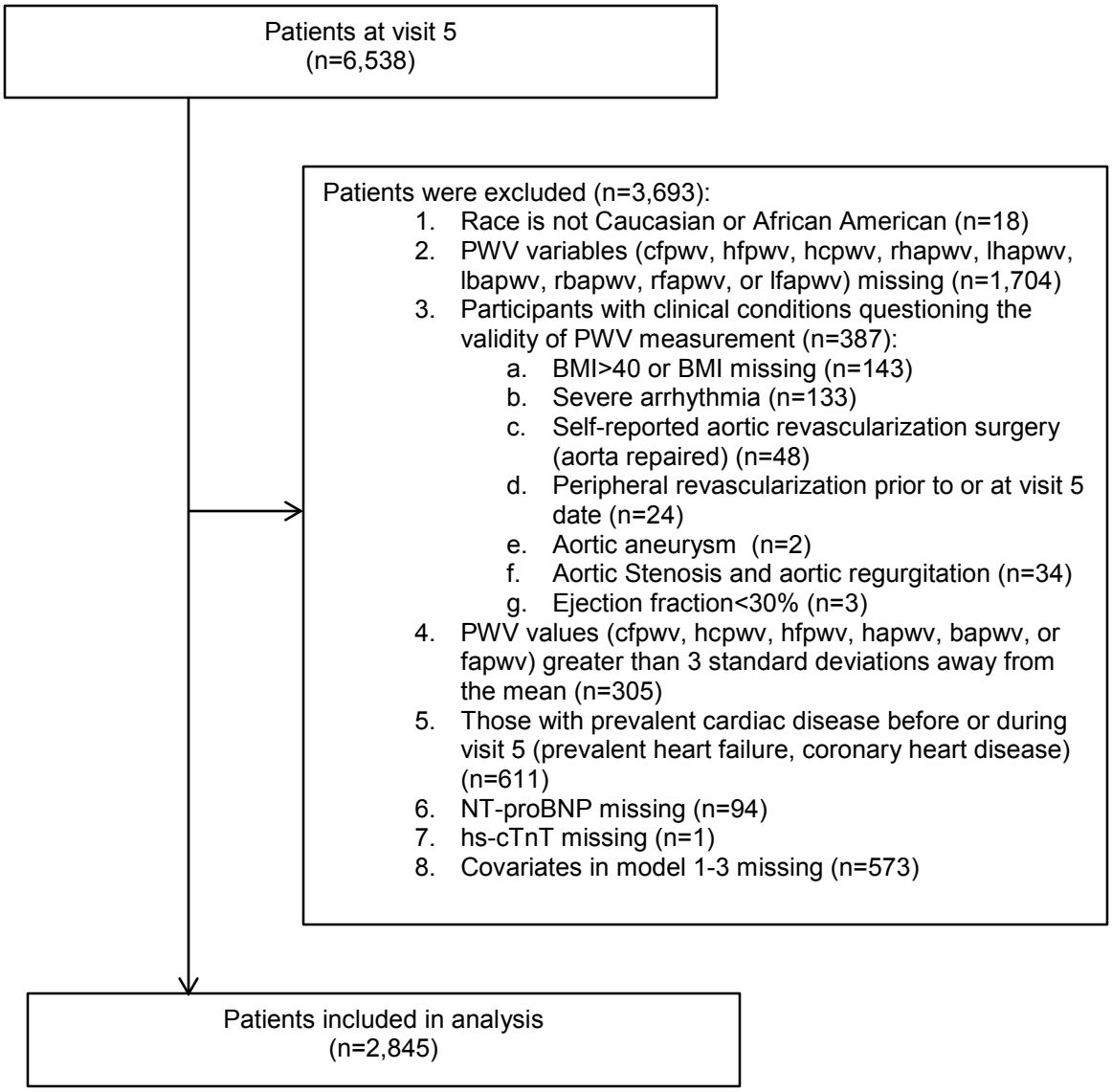
baPWV: Q1, ≤1538 (n=712); Q2, 1538-≤1728 (n=711); Q3, 1728-≤1948 (n=713); Q4, >1948 (n=709)

faPWV: Q1, ≤999 (n=713); Q2, 999-≤1108 (n=711); Q3, 1108-≤1224 (n=713); Q4, >1224 (n=708)

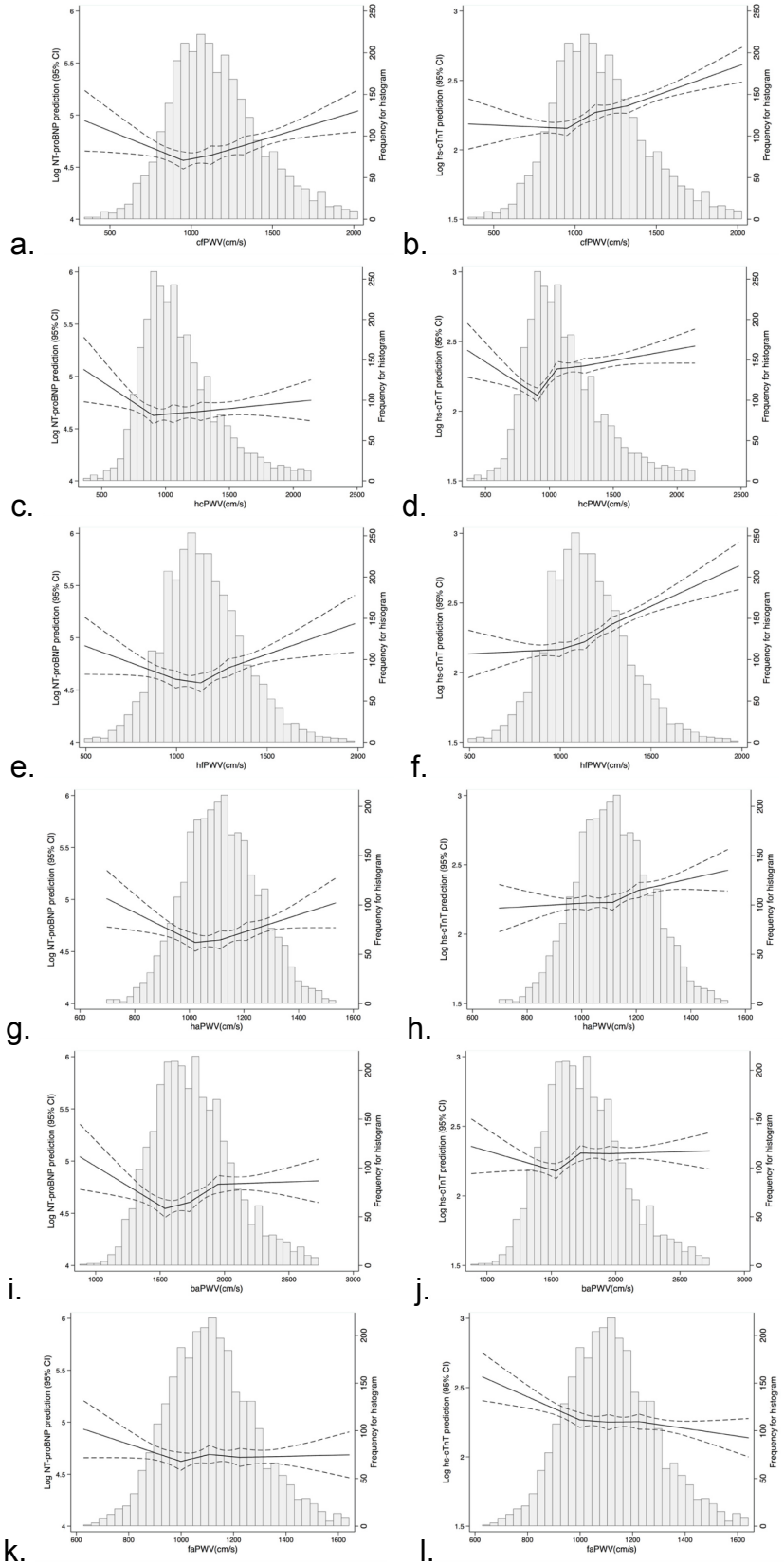
c. Odds ratio in logistic regression: It indicates the ratio of odds for elevated hs-cTnT level between each PWV quartile category and the reference category (Q2). Odds ratio > 1 means higher odds for elevated hs-cTnT level in the quartile category comparing to the reference group.

*P<0.05.

Supplementary Figure 1. Study flow chart



Supplement Figure 2. Predicted log NT-proBNP and hs-cTnT with regional PWV with splines by quartiles without adjustment



Curriculum Vitae

SHUIQING LIU

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Master of Health Science candidate studying clinical epidemiology with a strong focus towards epidemiological and biostatistical methods and data analysis. Lead researcher with experience in both epidemiology and biostatistics. Teaching assistant and international volunteer serving medical support in Nepal. Fluent in English and Chinese.

EDUCATION

Master of Health Science (MHS) Expected Aug 2016
Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD, USA
Concentration (Track): Epidemiology (Clinical Epidemiology)

Bachelor of Medicine, Bachelor of Surgery (MBBS) July 2014
Peking University (PKU), Beijing, China

AWARDS AND SCHOLARSHIP

Master's Tuition Scholarship	Sep 2015
Center for Clinical Trials and Evidence Synthesis (CCTES) Student Funding	Apr 2015
Funding for PKUHSC Students Innovation Research and Training	May 2013
China Medical Board (CMB) Educational Reform Project Funding	Sep 2012
Scholarship for Outstanding Medical Students, Peking University	2010 – 2011

RESEARCH EXPERIENCE

Lead Researcher Dec 2015 – present
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
Master thesis title: *Segment-specific Pulse Wave Velocity and Subclinical Cardiac Overload and Damage in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study*

- Conducted literature review for 55 studies and data abstraction for 28 studies
- Compiled 4 datasets including 463 variables and 15700 patients, using Stata version 13.0
- Quantified the association between pulse wave velocity (PWV) and cardiac biomarker NT-proBNP and hs-cTnT using multivariate linear regression model and logistic regression model, using Stata 13.0
- Wrote an ARIC manuscript proposal and a manuscript for the study

Achievements

- Found the importance of central arterial stiffness over peripheral arterial stiffness in the development of subclinical cardiac overload

Lead Researcher Aug 2015 – Nov 2015
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
Project title: *Longitudinal analysis: Weight Change and Glomerular Filtration Rate (GFR) in Children with Chronic Kidney Disease (CKD)*

- Using multivariate linear mixed-effect model with random intercept and random slope for time from baseline to examine the between-individual association between baseline weight percentile and GFR, and the within-individual association between change in weight percentile from baseline and GFR, separately, using Stata13.0
- Checked interaction between time from baseline and weight percentile change from baseline using an extended mixed-effect model with an additional interaction term

Achievements

- Found that in non-glomerular CKD group, between individuals, a higher baseline weight percentile was significantly associated with higher GFR ($P<0.05$).

Research Assistant Mar 2015 – Present

Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Project title: *Using Pooled Proportions in Sample Size Calculation for Binary Outcomes in Clinical Trials*
Project title: *A Systematic Review and Meta-analysis: Effects of Warfarin Use on Stroke, Bleeding, and Mortality Outcomes in Patients with End Stage Renal Disease and Atrial Fibrillation (dates)*
Project title: *A Systematic Review of Randomized Controlled Trials: Efficacy of Healthcare Interventions for Management of Dyspnea for Cancer Patients*
Project title: *A Systematic Review and Meta-analysis: Metformin and Cancer Risk, Taking into Account Biases and Confounders*
Project title: *Lens Extraction for Chronic Angle-closure Glaucoma (Review)*

- Assisted with literature review on sample size calculation for binary outcomes in clinical trials
- Assisted searching 7,154 studies from Pubmed, Embase and Central database; completed title/abstract screening for 5,798 studies and full-text screening for 123 studies
- Abstracted data from 80 studies in terms of study design, biases and study result; generated forest plot using Review Manager 5.0

Data analyst May 2015 – Sep 2015

Johns Hopkins Department of Orthopaedic Surgery, Baltimore, USA

Project title: *Primary versus Revision Surgery for Adult Spinal Deformity: an Analysis of Cost Effectiveness*

- Imported the dataset of 140 patients with 50 health- and surgery-related variables from Excel to Stata; conducted a multiple monotone imputation for missing values.
- Estimated quality-of-life EuroQol-5 Dimensions (EQ-5D) using published equations and calculated quality-adjusted life-years (QALYs) and cost/QALY gain ratios, using Stata software version 12.0
- Compared QALY and cost/QALY gain ratios in two cohorts using Mann-Whitney nonparametric statistic, Compared categorical parameters using Pearson's chi-square test ($\chi 2$)
- Assisted writing the statistical analysis and result parts in the manuscript

Lead Researcher May 2012 – Jul 2014

Peking University Health Science Center, Beijing, China

Project title: *A Meta-analysis of Randomized Controlled Trials: Mirena (Levonorgestrel-Releasing Intrauterine System) versus T Copper Devices for Contraception*

- Designed the research proposal; searched for 685 studies and included 10 studies
- Assessed the risk of bias using the Cochrane domain-based evaluation;
- Analyzed treatment effect, dichotomous data and heterogeneity using Review Manager 5

Achievements

- Found that Mirena results in lower accidental pregnancy and expulsion rates but exerts more influence on menstrual bleeding patterns and length than T copper devices

TEACHING EXPERIENCE

Teaching Assistant Aug 2015 – Mar 2016

Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Course title: 140.623 Statistical Methods in Public Health I-III

- Held and participated in TA office hours and Stata help sessions
- Worked with faculty members in grading homework and exams

PUBLIC HEALTH/CLINICAL INTERNSHIP

Intern Aug 2013 – Oct 2013

Centers for Disease Control and Prevention, Beijing, China
- Completed a 3-month rotation in the Statistic Information Department and AIDS/STD Prevention and Control Department
- Interviewed HIV carriers about their medical history; helped with data collection

Intern Sep 2012 – Jan 2013
Peking University Ninth Hospital, Beijing, China
- Completed a 4-month clinical rotation
- Assisted in surgeries and inquired with patients about medical history
- Completed case reports and acquired basic clinical skills

MEDICAL VOLUNTEER EXPERIENCE

International Medical Volunteer Jul 2012 – Aug 2012
We Women Clinics, Banepa, Kathmandu, Nepal
- Administered injections and took blood pressure measurements
- Gave lectures on family planning and HIV/AIDS prevention
- Provided pregnancy tests for local women
- Assisted in surgery of subcutaneous implants for contraception

PUBLICATIONS

1. Golozar A, **Liu S.**, Lin JA., Peairs K., Yeh HC. Does Metformin Reduce Cancer Risks? Methodologic Considerations. *Curr Diab Rep.* 2016 Jan;16(1):4.

2. Zhou H., Zhang L., Ye F., Wang HJ., Huntington D., Huang Y., Wang A., **Liu S.**, Wang Y. The Effect of Maternal Death on the Health of the Husband and Children in a Rural Area of China: A Prospective Cohort Study. *PLoS One.* 2016 Jun 9;11(6):e0157122.

3. **Liu, S.**, Wang, T., Wang, Y., Liu, Y., Zhan, Y., Huang, Q., Mo, Y. and Wang T. (under revision). An Investigation on the Sleep Quality and Influential Factors among the Elderly in Nursing Homes of One District in Beijing.

4. **Liu, S.**, Wu, A., Meyer, M., Cheng, S., Hoogeveen, R., Ballantyne, C., Tanaka, H., Heiss, G., Selvin, E. and Matsushita, K. (in preparation). Segment-specific Pulse Wave Velocity and Subclinical Cardiac Overload and Damage in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

PROFESSIONAL DEVELOPMENT

- **Language:** Chinese (fluent), English (fluent)
- **Computer proficiency:** R programming, Stata programming, SAS programming, SPSS, SRDR, Review Manager Software, Microsoft Office Suite
- **Memberships:** Society for Clinical Trials